

REMARKS

Claim Amendments

By the present amendment, claims 1, 6-16 and 18-21 have been deleted, and claims 2-5 and 17 have been amended. The amendments have been made without prejudice, and without acquiescing to any of the Examiner's objections. The amendment does not contain new matter. The Office Action dated March 28, 2001 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Related Applications

As requested by the Examiner, the disclosure has been amended at Page 1 in order to include the status and the relationship of the present application to the prior applications.

Non-Elected Claims

Claims 1, 6-16 and 18-21 have been deleted by the present invention as they are related to a non-elected invention, and have been withdrawn for further consideration by the Examiner. These claims have been deleted without prejudice and applicant preserves the right to file these claims in a further divisional application.

Drawings


We note the objection to the drawings, and will submit from the drawings once the application is in order for allowance.

Abstract

We are not sure why the Examiner does not have an abstract as it was filed with the present application. A copy of the original abstract is also being submitted herewith.

37 CFR1.821d

Claims 4 and 5 have been amended in order to insert the SEQ ID. NOS. as requested. The Disclosure has also been amended in order to insert the



SEQ.ID.NOS. as requested by the Examiner. Applicant is simultaneously filing herewith a revised Sequence Listing which includes all of the sequences in the application.

Applicant is also submitting a Sequence Listing in computer readable form (a 3.5" floppy diskette) in the ASCII format. In accordance with the requirements of 37 C.F.R. 1.821-1.825 the undersigned verifies that the paper form of the Sequence Listing and the computer readable form of the Sequence Listing are the same.

Dependent Claims

Claims 3 and 17 have been amended in order to reflect the limitations of non-elected claims 1 and 15, respectively as requested by the Examiner.

35 USC §112, First Paragraph

(1) Written Description

The examiner has objected to claims 2, 3 and 17 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. We respectfully disagree with the Examiner for the reasons that follow.

Claims 2, 3 and 17 are directed to a method of preventing or reducing fetal loss comprising administering an effective amount of Fgl2 inhibitor. It is critical to point out that the Applicant is not attempting to claim Fgl2 inhibitors per se. In making the objection, the Examiner asks Applicant to direct its attention to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112 ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 (hereinafter "the Guidelines"). We respectfully submit that the Examiner is applying the Guidelines in the present case using the principles that were established when examining claims to novel nucleic acid or protein sequences. As the examiner is aware, the Guidelines were prepared as a result of a decision that

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dealt with whether or not the disclosure of a rat sequence was sufficient written description for a claim that related to the sequence from all vertebrates (University of California v. Eli Lilly, CAFC, 43 USPQ 2d 1398, 1997). This case dealt with the claims that related to nucleic acid molecules per se and not to uses of the nucleic acids or proteins. In the present case, Applicant is not trying to claim the genus of Fgl2 inhibitors, only to claim the method of prevention and reduction of fetal loss using such inhibitors. In particular, main claim 2 reads,

"A method of preventing or reducing fetal loss comprising administering an effective amount of an inhibitor of Fgl2 to an animal in need thereof."

Therefore, the invention recited in claim 2 relates to the demonstration by the inventors that inhibiting Fgl2 could prevent fetal loss. The application definitely provides a sufficient written description to inform a skilled artisan that Applicant was in possession of the claimed invention as whole at the time the application was filed. The claims under examination are directed to a single embodiment (e.g. prevention of fetal loss by inhibiting Fgl2) and not a genus as the Examiner appears to have concluded. Therefore, the guidelines used for examination of the present claims should be "for each claim drawn to a single embodiment or species" and not "for each claim drawn to a genus" (see the Guidelines, p.1106). Under this guideline, if the application describes an actual reduction to practice of the claimed invention, it will qualify as fulfilling the written description requirement. It is not necessary to include a description of a representative number of species. }

The Examiner suggests that the Applicant's disclosure is limited to inhibitors of Fgl2 which include antisense DNA specific for the polynucleotides of SEQ ID NO: 1 and 3 and antibodies specifically directed against sequences of 364-378 of SEQ ID NO:2 and 4. We disagree as these inhibitors were merely examples of functional inhibitors and were not intended to be exhaustive of the field of claimed inhibitors. In addition,

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the disclosure is clear that the invention is not intended to be limited to those specific antibodies and antisense molecules. For example, the application provides ample disclosure on page 6-11 on how other antibodies and antisense molecules can be prepared. Further, on page 11-12, it is clearly stated that other substances that inhibit Fgl2 may be isolated and used in the method of invention.

In summary, the disclosure of the application makes it clear that applicant was in possession of the invention, (which relates to a novel method for preventing or reducing fetal loss by inhibiting Fgl2), at the time of filing the application. Applicant has provided examples of antibodies and antisense molecules that can be useful in the invention. Applicant is not required to exemplify every possible Fgl2 inhibitor in the application in order to demonstrate that they were in possession of the invention as the invention relates to a novel method for preventing or treating fetal loss and not to novel Fgl2 inhibitors.

In view of the foregoing, we respectfully submit that the disclosure of the application is sufficient in order to meet the Written Description Guidelines. Consequently, we respectfully request that the objections to claims 2, 3, and 17 under 35 USC §112, first paragraph be withdrawn.

(2) Enablement

The Examiner has further objected to claims 2-5 and 17 under 35 USC §112, first paragraph as not being enabling for use of any antibody to Fgl2. We respectfully disagree with the Examiner for the reasons that follow.

The Examiner is suggesting that the specification only provides enablement for an antibody which recognizes an epitope of amino acids 364-368 of SEQ.ID.NO.2 and 4. We disagree as the Applicant has provided a very comprehensive description on pages 6-9 of how one skilled in the art could go about preparing other antibodies to Fgl2. Preparation of other antibodies would not require undue experimentation.

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The Examiner directs the Applicant to the decision of In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), which sets out the factors to be considered in determining whether undue experimentation is required, including the scope of the claim, the amount of direction or guidance provided, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The Examiner finds that it is difficult to determine which other antibodies would function in treating or preventing fetal loss. We respectfully disagree with the Examiner that undue experimentation is required to carry out the claimed invention.

As stated above, a person skilled in the art could readily prepare an Fgl2 antibody especially with reference to the disclosure. Once a person skilled in the art prepares an Fgl2 antibody as described in the application, the antibody could readily be tested for its ability to prevent or reduce fetal loss with the teachings of the disclosure. For example, the Applicants describe on page 39 of the specification, Examples 4 and 5, a detailed description of the methods for testing the effectiveness of an Fgl2 inhibitor, providing sufficient direction and guidance for one skilled in the art to reproduce the invention. Example 4 describes the method for determining the inhibitory effect on mice, which are stressed in order to induce fetal loss. As stated in the specification, the methodology has been well defined. This method does not require undue experimentation, it is simply an assay for the effectiveness of an inhibitory molecule (nucleic acid, protein or antibody), which can be determined easily by comparing the number of resorbing sites on day 13.5 of pregnancy in treated and untreated animals. Example 5 is similar but utilizes TNF- α and γ -IFN to induce fetal loss. Again, the resorption rate is used as an index of antibody/inhibitor effectiveness. All mice are examined at day 13.5, which is a relatively short experimentation time. Furthermore, in the decision of In re Colianni (561 F.2d 220,224, 195 USPQ 150, 153 (CCPA 1977)), which is referred to in MPEP 2164.06, the court states that "an extended period

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of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In the present case, there is sufficient direction and guidance, the experimentation required is well known in the art and the time for experimentation is relatively short.


In addition to the fact that the disclosure enables the preparation of Fgl2 inhibitors, others have prepared Fgl2 inhibitors. For example, Ning et al. (J. of Immunology, 1998, 160: 3487-3493) demonstrate that Ribavirin, a synthetic guanosine analogue, inhibits the expression of MHV-3-induced mRNA of Fgl2. Marazzi et al. (J. of Immunology, 1998, 161: 138-147), who are interested in the role of fgl-2 (fibroleukin) in T-lymphocytes, have prepared monoclonal antibodies to peptides from the carboxyl-terminal end of the deduced protein as well as to a recombinant protein fragment expressed in E. coli. These papers demonstrate that one skilled in the art could readily isolate Fgl2 inhibitors that may be useful in the present invention.

In view of the foregoing, we respectfully submit that the claims are enabled by the disclosure. Consequently, we respectfully request that the objections to claims 2-5 and 17 under 35 USC §112, first paragraph be withdrawn.

35 USC §112, Second Paragraph

The Examiner has objected to claims 2-5 and 17 under 35 USC §112, second paragraph as being indefinite or failing to particularly point out and distinctly claim the subject matter with which applicant regards as the invention. In particular, the Examiner states that the recitation of "amino acids at positions 364-368...in Figure 5" is ambiguous. In response, the recited amino acid sequence has been inserted into the Sequence Listing and is now referred to by a SEQ.ID.NO. 18.

The Examiner objects to claim 17 as reciting a composition that only a compound is disclosed. In response, claim 17 has been amended in order to properly recite a composition.



The Examiner has objected to claims 2-5 and 17 as being ambiguous in view of the recitation of "the method of treating fetal loss". In response, claims 2 and 17 have been amended in order to replace the term "treating" with the term "reducing".

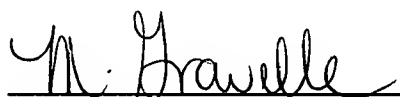
In view of the foregoing, we respectfully request that the objections to the claims under 35 USC §112, second paragraph be withdrawn.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested.

Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact **Micheline Gravelle** by telephone at **416-957-1682** at her convenience.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In The Disclosure:

Paragraph beginning at page 1, line 1 has been amended to read as follows:

This application is a continuation of PCT/CA98/00475, filed May 15, 1998, which claims priority to provisional application 60/061684 filed October 10, 1997 (now abandoned) and provisional applications 60/046,537 filed May 15, 1997 (now abandoned).

Paragraph beginning at page 4, line 35, has been amended to read as follows:

Figure 2 shows the nucleotide sequences of exon 1 of the mouse (SEQ.ID.NO.: 5) and human (SEQ.ID.NO.: 6) Fgl3 genes;

Paragraph beginning at page 4, line 37, has been amended to read as follows:

Figure 3 shows the nucleotide sequences of exon 2 of the mouse (SEQ.ID.NO.: 7) and human (SEQ.ID.NO.: 8) Fgl2 genes;

Paragraph beginning at page 5, line 1, has been amended to read as follows:

Figure 4 shows the nucleotide sequence of the 3' UTR of hFgl2 (SEQ.ID.NO.: 9);

Paragraph beginning at page 5, line 2, has been amended to read as follows:

Figure 5 shows the amino acid sequences of the mouse (SEQ.ID.NO.: 4) and human (SEQ.ID.NO.: 2) Fgl2 proteins with the serine protease sites boxed;

Paragraph beginning at page 5, line 7, has been amended to read as follows:

Figure 8 shows the nucleotide sequence of the mouse (SEQ.ID.NO.: 10) and human (SEQ.ID.NO.: 11) Fgl2 gene promoter regions;

Paragraph beginning at page 5, line 9, has been amended to read as follows:

Figure 9 shows the nucleic acid sequence of the transcription binding sites in the putative promoter region of *hfgl2* (SEQ.ID.NO.: 12);

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Paragraph beginning at page 5, line 22, has been amended to read as follows:

Figure 17 shows the Fgl-2 promoter DNA sequence (SEQ.ID.NO.: 13).

Paragraph beginning at page 7, line 7, has been amended to read as follows:

The present invention also provides an antibody that binds an epitope of hFgl2 comprising the amino acids at positions 300 to 400 in Figure 5. In a preferred embodiment, the present invention provides an antibody that binds an epitope of hFgl2 comprising the amino acids at positions 364-378 (DRYPSGNCGLYYSSG) (SEQ.ID.NO.: 18) in Figure 5.

Paragraph beginning at page 18, line 6, has been amended to read as follows:

As hereinbefore mentioned, the present inventor has cloned and sequenced genomic *hFgl2*. In this regard, the entire genomic sequence as well as the sequence of the promoter region, shown in Figure 8 (SEQ.ID.NO.: 11), and the 3' UTR, shown in Figure 4 (SEQ.ID.NO.: 9), are included within the scope of the invention.

Paragraph beginning at page 18, line 10, has been amended to read as follows:

Accordingly, in one embodiment the present invention provides an isolated nucleic acid molecule comprising (a) the sequence shown in Figure 8 (SEQ.ID.NO.: 11), where T can also be U; (b) nucleic acid sequences which have substantial sequence identity with (a); and (c) a fragment of (a) or (b).

Paragraph beginning at page 18, line 14, has been amended to read as follows:

In another embodiment the present invention provides an isolated nucleic acid molecule comprising (a) the sequence shown in Figure 4 (SEQ.ID.NO.: 9), where T can also be U; (b) nucleic acid sequences which have substantial sequence identity with (a); and (c) a fragment of (a) or (b).

Paragraph beginning at page 18, line 18, has been amended to read as follows:

The present invention also includes fragments of the nucleic acid sequences shown in Figure 2 or 3 or [SEQ.ID.NO.:1 or 3] SEQ.ID.NOS.:6 or 8 which have particular utility in the methods and compositions described above. The fragments generally comprise a nucleic acid sequence having at least 15 bases which will hybridize to the sequences shown in Figures 2 and 3 or [SEQ.ID.NO.:1 or 3] SEQ.ID.NOS.:6 or 8 under stringent hybridization conditions.

Paragraph beginning at page 19, line 7, has been amended to read as follows:

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Further, it will be appreciated that the invention includes nucleic acid molecules comprising nucleic acid sequences having substantial sequence identity with the nucleic acid sequences shown in Figures 2 (SEQ.ID.NO.: 6), 4 (SEQ.ID.NO.: 9) and 8 (SEQ.ID.NO.: 11) and fragments thereof having at least 15 bases which will hybridize to these sequences under stringent hybridization conditions. The term "sequences having substantial sequence identity" means those nucleic acid sequences which have slight or inconsequential sequence variations from the sequences disclosed in Figures 2 (SEQ.ID.NO.: 6) and 3 (SEQ.ID.NO.: 8), i.e. the sequences function in substantially the same manner to produce substantially the same activity as described herein for Fgl2. The variations may be attributable to local mutations or structural modifications. Nucleic acid sequences having substantial identity include nucleic acid sequences having at least 72%, preferably at least 75-95% identity with the nucleic acid sequences as shown in Figure 2 (SEQ.ID.NO.: 6) and Figure 3 (SEQ.ID.NO.: 8).

Paragraph beginning at page 19, line 18, has been amended to read as follows:

Isolated and purified nucleic acid molecules encoding a protein having the activity of human Fgl2 as described herein, and having a sequence which differs from the nucleic acid sequence shown in Figure 2 (SEQ.ID.NO.: 6) and Figure 3 (SEQ.ID.NO.: 8) due to degeneracy in the genetic code are also within the scope of the invention. Such nucleic acids encode functionally equivalent proteins (e.g., a protein having human Fgl2 prothrombinase activity) but differ in sequence from the sequence of Figure 2 (SEQ.ID.NO.: 6) and Figure 3 (SEQ.ID.NO.: 8) due to degeneracy in the genetic code.

Paragraph beginning at page 19, line 32, has been amended to read as follows:

The nucleic acid molecules of the invention can be used to isolate an *Fgl2* from other species. For example, a labelled nucleic acid probe based on all or part of the nucleic acid sequence shown in Figure 2 (SEQ.ID.NO.: 6) and 3 (SEQ.ID.NO.: 8) can be prepared, and used to screen an appropriate DNA library (e.g. a cDNA or genomic DNA library). Nucleic acids isolated by screening of a cDNA or genomic DNA library can be sequenced by standard techniques.

Paragraph beginning at page 20, line 19, has been amended to read as follows:

The initiation codon and untranslated sequences of human Fgl2 may be determined using currently available computer software designed for the purpose, (e.g. PC/Gene (IntelliGenetics Inc., Calif.). The nucleic acid sequence for a 3' untranslated region of *hfgl2* is shown in Figure 4 (SEQ.ID.NO.: 9). The intron-exon structure and the transcription regulatory sequences of the gene encoding human Fgl2 may be identified by using a nucleic acid molecule of the invention encoding human Fgl2 to probe a genomic DNA clone library. Regulatory elements can be

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identified using conventional techniques. The function of the elements can be confirmed by using them to express a reporter gene such as the bacterial gene lacZ which is operatively linked to the elements. These constructs may be introduced into cultured cells using standard procedures or into non-human transgenic animal models. Such constructs may also be used to identify nuclear proteins interacting with the elements, using techniques known in the art.

Paragraph beginning at page 20, line 31, has been amended to read as follows:

In addition to the full length amino acid sequence (Figure 5), the proteins of the present invention include truncations and analogs, and homologs of the protein and truncations thereof as described herein. A truncated Fgl2 protein or fragment of the human Fgl2 protein is a portion of the full-length Fgl2 amino acid sequence having one or more amino acid residues deleted. The deleted amino acid residue(s) may occur anywhere in the polypeptide, including at either the N-terminal or C-terminal end or internally. Fgl2 fragments typically will have a consecutive sequence of at least 10, 15, 20, 25, 30, or 40 amino acid residues that are identical to the sequences of the human Fgl2. The truncations or portions of the Fgl2 protein may comprise an antigenic site that is capable of cross-reacting with antibodies raised against the Fgl2 protein whose sequence is shown in Figure 5 (SEQ.ID.NOS: 2 and 4). Therefore, immunogenic portions or fragments of human Fgl2 proteins are within the scope of the invention (e.g. amino acids 300 to 400 in Figure 5). Preferably the truncated protein or portion of the protein binds with an affinity of at least about 10^6 L/mole to an antibody raised against human Fgl2.

Paragraph beginning at page 21, line 14, has been amended to read as follows:

The proteins of the invention may also include analogs of human Fgl2 as shown in Figure 5 (SEQ.ID.NOS: 2 and 4) and/or truncations thereof as described herein, containing one or more amino acid substitutions, insertions, and/or deletions. Amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions involve replacing one or more amino acids with amino acids of similar charge, size, and/or hydrophobicity characteristics. When only conserved substitutions are made the resulting analog should be functionally equivalent to human Fgl2 as described herein. Non-conserved substitutions involve replacing one or more amino acids with one or more amino acids which possess dissimilar charge, size, and/or hydrophobicity characteristics.

Paragraph beginning at page 21, line 23, has been amended to read as follows:

One or more amino acid insertions may be introduced into the amino acid sequence as shown in Figure 5 (SEQ.ID.NOS: 2 and 4). Amino acid insertions may consist of single amino acid residues or sequential amino acids ranging from 2 to 15

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amino acids in length. For example, amino acid insertions may be used to destroy the prothrombinase activity of the protein.

Paragraph beginning at page 21, line 27, has been amended to read as follows:

Deletions may consist of the removal of one or more amino acids, or discrete portions (e.g. amino acids) from the human Fgl2 amino acid sequence as shown in Figure 5 (SEQ.ID.NOS: 2 and 4). The deleted amino acids may or may not be contiguous. The lower limit length of the resulting analog with a deletion mutation is about 10 amino acids, preferably 100 amino acids.

Paragraph beginning at page 21, line 32, has been amended to read as follows:

The proteins of the invention also include homologs of human Fgl2 as shown in Figure 5 (SEQ.ID.NOS: 2 and 4) and/or truncations thereof as described herein. Such homologs are proteins whose amino acid sequences are comprised of the amino acid sequences of human Fgl2 regions from other species that hybridize under stringent hybridization conditions (see discussion of stringent hybridization conditions herein) with a probe used to obtain human Fgl2 as shown in Figure 5 (SEQ.ID.NOS: 2 and 4). It is anticipated that a protein comprising an amino acid sequence which is at least 72% preferably 75 to 90% similar, with the amino acid sequence shown in Figure 5 (SEQ.ID.NOS: 2 and 4) will exhibit prothrombinase activity.

Paragraph beginning at page 23, line 36, has been amended to read as follows:

Human genomic DNA from the liver was amplified by Polymerase Chain Reaction using primers specific to the human cDNA sequence obtained from GenBank, that corresponds to exon 2 of mouse fgl2 gene; the sense primer CAA AAG AAG CAG TGA GAC CTA CA (SEQ.ID.NO.: 14) (hufpl7) is at position 692, and the antisense primer TTA TCT GGA GTG GTG AAA AAC TT (SEQ.ID.NO.: 15) (hufpl8) is at position 1133 of the human cDNA. The PAC library, from Genome Systems Inc. (St. Louis, Missouri), was screened using the single amplicon, of about 300 nucleotides in length, that was produced from the above Polymerase Chain Reaction. Three clones, namely 6359, 6360, and 6361 were found positive for this screening. The plasmids containing these three clones were purified using the Qiagen maxiprep DNA purification protocol. The quality of the purified DNA and the presence of the inserts were verified by digesting the plasmid with Not 1 restriction enzyme (Canadian Life, Burlington, Canada), and subjecting the samples to Clamped Homogenous Electric Field (CHEF) gel electrophoresis, at 120 angle, 6 Volts, 1-20 seconds ramp interval, 0.5X TBE, and run time of 18 hours.

Paragraph beginning at page 24, line 13, has been amended to read as follows:

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The clone 6360 was chosen for the rest of the study because in a dot blot analysis it consistently hybridized to sense primer GCA AAC AAT GAA ACA GAG GAA A (SEQ.ID.NO.: 16) (huflp1) at position 100 and anti-sense primer at position ATT GCC CTA TTA GAT AAC GAA TAC (SEQ.ID.NO.: 17) (huflp2) at position 1400. In order to reduce the DNA into fragments of 5 to 10 kb, which is a convenient size range to work with, the 6360 clone was digested under sub-optimal conditions with the restriction enzyme Sau 3A (Canadian Life, Burlington, Canada). The appropriate digest condition was found by incubating 5 µg of DNA with 1 µl of 2 µ/µl, 0.5 µ/µl, and 0.1 µ/µl of Sau 3A for one hour, at 37°C in a total reaction volume of 20 µl and observing the size range of the DNA fragments on a CHEF gel; the run conditions are 1 to 10 seconds ramp interval, 4.5 volts, 120 angle, 0.5X TBE, and a run time of 16 hours. The 6360 clone was large scale restriction digested by proportionately increasing the amount of DNA, reaction volume, and the amount of enzyme, that is, 10 µg, 40 µl, and 2 µl respectively. The final products of the restriction digest were subjected to CHEF gel electrophoresis at the above conditions. The DNA band corresponding to 6-9kb was excised and fragments were extracted using the Gene Clean DNA purification kit (Bio/Can Scientific, Mississauga, Ontario). The fragments were ligated into the alkaline phosphatase (Pharmacia, Uppsala, Sweden) treated BamH1 site of the Bluescript II vector (Stratagene) and transfected into DH10B competent cells by electroporation. This Bluescript II library was screened using the huflp1 and 2 primers. The primers were labeled at the 5 end with gamma P32 by using the enzyme Polynucleotide Kinase (Pharmacia, Uppsala, Sweden); these primers were used to screen the Bluescript library. The clone J14 hybridized to both these primers and was used for the subsequent work.

Paragraph beginning at page 27, line 24, has been amended to read as follows:

An AP1 site is located about 20 nucleotides from the TATA box (Figures 8 and 9). The consensus for AP1 motif is TGASTCA (SEQ.ID.NO.: 19), where S is a guanine or a cytosine. Except for the central S, cytosine in humans and guanine in mouse, the AP1 site is identical in mouse and human direct prothrombinase genes. AP1 is composed of dimers of proteins of the Fos and Jun proto-oncogene families. The Jun family members are DNA binding proteins; they bind to the AP1 site as homodimers or as heterodimers with Fos members. Upon activation, Jun gets dephosphorilated at a site proximal to DNA binding domain and acquires its ability to bind DNA (Curran and Fianza, 1988; Woodgett et al., 1995). Furthermore, the transactivating domains of Fos and Jun get phosphorylated and are able to interact with the transcription machinery (Woodgett et al., 1995). In certain genes such as tissue factor gene, the AP-1 is required for both constitutive and induced expression (Mackman et al., 1989; Moll et al., 1995).

Paragraph beginning at page 33, line 25, has been amended to read as follows:

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DNA from -3.5kb/+9bp and -1.3kb/+9bp fgl-2 promoter region pGL-2-Basic luciferase constructs (pL-3500, pL-1300) was obtained from clones previously constructed in Dr. Levy's lab (unpublished data). Additional 5' truncation series plasmids and the 3' pL3'274 luciferase vector were constructed first using PCR, followed by cloning into a PCR2.1 plasmid (Invitrogen). Specific portions of the pL-3500 clone were amplified at 35 cycles performed at 95 C for 1 min, 58 C for 1 min, 72 C for 2 min. The downstream 3' reverse primer, present in pGL2-Basic, was fixed for all 5' truncations and was 5'-GAA ATA CAA AAA CCG CAG AAG G-3' (SEQ.ID.NO.: 20) (Promega). The upstream primer used to construct pL-995 was 5'TCT TGG GAA ATC TGG TTA GAG-3 (SEQ.ID.NO.: 21). The upstream primer for pL-681 was 5'-GAG CTG AGT GAT GGG GAA GGA-3' (SEQ.ID.NO.: 22). The upstream primer for pL-294 was 5'-GGG CAC TGG TAT TAC AAC TGT-3' (SEQ.ID.NO.: 23), and the 5' primer for pL-119 was 5'-CTC CTC CTG TGT GGC GTC TGA-3' (SEQ.ID.NO.: 24). The fixed 5' forward primer for the 3' truncation was 5'-GGA TAA GGA GGG CAG GGT GAA-3' (SEQ.ID.NO.: 25). The downstream antisense primer for pL3'274 was 5'-ACA GTT GTA ATA CCA GTG CCC-3' (SEQ.ID.NO.: 26). Following PCR, PCR products were ligated and cloned into the PCR2.1 vector. PCR2.1 clones were sequenced to check for orientation, and DNA was obtained from desired clones. For the 5' truncations, the PCR2.1 clones were digested with KpnI and Sall, and then ligated and cloned into the pGL2-Basic luciferase vector (Promega) cut with KpnI and XhoI. Each final construct was checked with a specific diagnostic digestion before maxi-preps of DNA were made. For pL3'274, PCR2.1 clones were digested with EcoRV and HindIII, and then ligated and cloned into pGL2-Basic cut with SmaI and HindIII. A summary of the different constructs produced is shown in Figure 13.

Table 3 beginning at page 55 has been amended to read as follows:

PRIMER	SEQUENCE	5' POSITION	tm 2(A+T)+4(G+C)
HUFLP1	GCA AAC AAT GAA ACA GAG GAA A (SEQ.ID.NO.: 16)	100	60
HUFLP2	ATT GCC CTA TTA GAT AAC GAA TAC (SEQ.ID.NO.: 17)	1399	64
HUFLP3	AAC GGA GAC CCA GGC AGA AAC (SEQ.ID.NO.: 27)	349	66
HUFLP4	CTT CGG GAG CTG AAT AGT CAA (SEQ.ID.NO.: 28)	243	62
HUFLP5	GAC AGC AAA GTG GCA AAT CTA (SEQ.ID.NO.: 29)	553	60
HUFLP6	TTC TGG TGA AGT TGG TGC TCC (SEQ.ID.NO.: 30)	832	64
HUFLP7	CAA AAG AAG CAG TGA GAC CTA CA (SEQ.ID.NO.: 31)	693	66
HUFLP8	TTA TCT GGA GTG GTG AAA AAC TT (SEQ.ID.NO.: 15)	1125	62
HUFLP9	TGA CCA AGA GTA AGG AAA TGA (SEQ.ID.NO.: 32)	908	58
HUFLP10	TGA CTG TAT TTG TTC TTG GCT G (SEQ.ID.NO.: 33)	639	62
HUFLP11	TTC TGG GAA CTG TGG GCT GTA (SEQ.ID.NO.: 34)	1134	64
HUFLP12	CCA GCT TCA TCT TTA CAG T (SEQ.ID.NO.: 35)	43	54
HUFLP13	AAT CAC TCT GTT CAT TCC TCC (SEQ.ID.NO.: 36)	1353	60
HUFLP14	GAA ATA ATA TGC ATT GAA A (SEQ.ID.NO.: 37)	-173	36
HUFLP14R	AAC GCA CAG GAA GAG GAG A (SEQ.ID.NO.: 38)	-96	58
HUFLP15	TTG ACA TCC TTT GAG ATA T (SEQ.ID.NO.: 39)	1459??	50
HUFLP16	ATG GGG CAT TGG GGA GC (SEQ.ID.NO.: 40)	-427	56
HUFLP17	GGC TAT CTC CTC TTC CTG T (SEQ.ID.NO.: 41)	-118	58
HUFLP18	TGA GCT ATG CCA GTG TCT GT (SEQ.ID.NO.: 42)	-755	60
HUFLP19	CAA GCG TAG TAT ACC AAA T (SEQ.ID.NO.: 43)	-288	52
HUFLP20	AAG GCA GGA AAG AGG AAC (SEQ.ID.NO.: 44)	-961	54
HUFLP21	GAC AAA GGA ATA GAA AGT AGC (SEQ.ID.NO.: 45)	-601	58
HUFLP22	CAG GGC AAA AAT CTA AAT G (SEQ.ID.NO.: 46)	-1092	52
HUFLP23	GCC CAG AGA GCA GGT AGA A (SEQ.ID.NO.: 47)	-883	60
HUFLP24	CCA GCC AGG GTT GAA ATA (SEQ.ID.NO.: 48)	3' end	54
HUFLP25	GCC CTG TCA GTC ATT TTG (SEQ.ID.NO.: 49)	promoter: not used	54
HUFLP26	AAA AAC CTA CCA GTA GTC T (SEQ.ID.NO.: 50)	3' end	52
HUFLP28	TTG GGG TGA CAT TAT GC (SEQ.ID.NO.: 51)	2399	50
HUFLP 29	TGA GCA GCA CTG TAA AGA TG (SEQ.ID.NO.: 52)	16	58
HUFLP30	GTG GCT TAA AGT GCT TGG GT (SEQ.ID.NO.: 53)	1350	60

In The Claims:

Claims 2, 3, 4, 5 and 17 have been amended as follows:

2. (Amended) A method of preventing or [treating] reducing fetal loss comprising administering an effective amount of an inhibitor of Fgl2 to an animal in need thereof.
3. (Amended) A method according to claim [1 or] 2 wherein said inhibitor is an antibody that binds to Fgl2.
4. (Amended) A method according to claim 3 wherein the antibody is a monoclonal antibody that binds to human Fgl2 having the amino acid sequence as shown in [Figure 5] SEQ.ID.NO. 2.
5. (Amended) A method according to claim 4 wherein the antibody binds an epitope of human Fgl2 comprising the amino acids at positions 364-378 DRYPSGNCGLYYSSG in [Figure 5] (SEQ.ID.NO. 18.)
17. (Amended) A method for [preventing or treating] reducing fetal loss in an animal comprising administering a therapeutically effective amount of a composition [as claimed in claim 15] comprising an antibody specific for an Fgl2 protein in admixture with a suitable diluent or carrier [or (b) an antisense oligonucleotide to Fgl2].